# SACHRP Recommendation Regarding Oversight of Research Misconduct and Regulatory Noncompliance

Over the past few months, SACHRP, both in its own sessions and in those of its Subcommittee on Harmonization, has considered the intersection of the jurisdictions, regulatory processes, and sanctions of the Office for Human Research Protections (OHRP) and the Office of Research Integrity (ORI). As described more fully herein, SACHRP also has noted this jurisdictional and procedural intersection in light of the proposed rule of the Food and Drug Administration relating to possible falsification of data by investigators. 75 Fed. Reg. 7412 (Feb. 19, 2010). These various regulatory regimes interact in complex ways with existing institutional processes for protecting human subjects, for preserving the reputation of the respondent, and for investigating allegations of research misconduct. Most importantly, the circumstances in which human subjects research may deviate from accepted professional standards do not necessarily respect the fine-grained distinctions between noncompliance under the Common Rule, research misconduct, and violations of FDA regulations. In our deliberations in this area, SACHRP has identified some significant disharmonies between these sets of procedures that govern (or in the case of the FDA's pending proposal, would govern) noncompliance with regulatory standards relating to research with human subjects. tSACHRP asks that these issues be addressed in unified or coordinated guidance from these agencies within the Department of Health and Human Services, or, to the extent necessary, by regulatory amendments.

According to presentations made to SACHRP by ORI representatives, ORI accepts jurisdiction over matters relating to possible fabrication, falsification, or plagiarism in research funded by the Public Health Service (PHS). Of course, alleged fabrication or falsification of data, or plagiarism of previous scholarly work and data may occur in any research, not limited to research with human subjects. In identifying categories of alleged violations that would be included in its jurisdiction, ORI historically has deferred to OHRP in certain matters relating to human subject research, consistent with OHRP's jurisdiction over possible violations of the Common Rule, 45 CFR 46. ORI has typically, for example, deferred to OHRP in relation to, among other matters, allegations of falsified or forged consent forms, failure to obtain informed consent, failure to report unanticipated adverse events, forging an investigator's signature, enrolling subjects who fail to meet eligibility criteria, and protocol deviations of other sorts. At the same time, ORI has reported that it would accept jurisdiction over allegations of substituting one research subject's record for another, changing research records to reflect desired data and results, altering subject eligibility test results, and falsifying dates on screening logs for prospective subjects.

1. Overlapping Regulatory Regimes of <u>OHRP, ORI and FDA</u>

SACHRP has presented a series of jurisdictional scenarios that would seem to illustrate the overlapping nature of noncompliance under the regulatory regimes overseen by OHRP, ORI and FDA. Among the scenarios that SACHRP has offered for discussion include:

- An investigator falsifies informed consent forms in a PHS-funded study in which informed consent has been described in detail in the research protocol approved by the IRB, but study subjects were otherwise treated appropriately. In publication, the human subjects section inaccurately describes the elaborate informed consent process that was described in the protocol and approved by the IRB, but that was not followed by the investigator. The IRB discovers this serious human subject research regulatory deviation, and requires that the investigator not use the collected data. The study, paid for with significant federal grant funds, is now worthless. There has been falsification of documents, with significant harm to research integrity and a waste of federal funds, all caused by significant deviations from an IRB-approved protocol.

- To achieve statistically significant results in an NIH-funded study, an investigator fabricates research data on 50 subjects, and reports enrollment as 100. Only 50 subjects actually enrolled and completed a complicated, lengthy protocol, and the protocol had no direct benefit to the subjects. The investigator combines the fabricated data on 50 fictitious subjects with actual data on the 50 true subjects, and publishes the results, which are then also used to support an FDA submission, This represents fabrication of data, deviation from an IRB-approved protocol that is so significant that it has destroyed the integrity of the study, and submission of false information to the FDA. This research misconduct would also seem to represent a serious violation of standards relating to human subjects research and of FDA regulations..
  Further, if subsequent studies (for example, the progression to phase II o r phase III studies) were premised on inaccurate results in this study, then subjects in the later studies would have been put at unjustifiable risk; the gravity of protocol deviations in this study would thus have been compounded by later reliance on study results, with subjects directly endangered.

- An investigator falsifies eligibility criteria information on enrollment forms for subjects, so that a full complement of subjects can be enrolled quickly. The study is conducted with multiple subjects whose eligibility criteria/enrollment forms were falsified. A research misconduct inquiry process, undertaken under ORI requirements, reveals this. Thereafter, disclosure is made to the IRB, leading to an IRB finding that multiple subjects who were actually ineligible for the study were subjected to serious and harmful research interventions. This incident of research misconduct also should be viewed as a violation of human subjects research standards under 45 CFR 46.

- In a study partially funded by NIH, an investigator fails to report serious and unexpected adverse events that are directly related to the test article. These serious and unexpected adverse events in turn were not reported in publications or in subsequent FDA submissions. The study publications and FDA submissions erroneously indicate, in fact, that few or no serious adverse events occurred during the study. This course of conduct by the investigator would seem to constitute FDA violations, research misconduct, and a violation of human subjects research standards.

2. Differences in Institutional Compliance with Processes, Standards and Enforcement

In such cases as those set forth above, processes for pursuing allegations of research misconduct, possible deviations from human subjects research standards, and FDA violations vary significantly.. FDA on-site enforcement actions and the relatively informal processes that may be employed by IRBs under the Common Rule tend to be much more rapid than the ORI-mandated processes of inquiry and investigation for possible research misconduct. Second, the burden of proof of violations and evidentiary standard are undefined under the Common Rule, but are designated as the "preponderance of evidence" under ORI's regulations. Third, OHRP generally enforces Common Rule standards against institutions, under the terms of their FederalWide Assurance (FWA), while ORI and FDA typically impose sanctions against individual investigators rather than research institutions, unless they also find failings in an institution's internal processes. Fourth, ORI processes stress the confidentiality of research misconduct proceedings and the need to protect an investigator's reputation, while FDA operates to enforce regulations of compelling public importance, and while Common Rule standards are much more concerned with protection of human subjects than with the peer and public perceptions of an investigator. Fifth, in order to establish research misconduct, there must be specific evidence of fabrication, falsification or plagiarism by an individual investigator, while FDA and Common Rule standards focus on violations of and deviations from standards, regardless of investigator intention and regardless of causation that is traceable to any identified individual..

Specifically, SACHRP has received comments from institutional officials whose internal compliance efforts in regard to human subjects research and research misconduct (as defined by ORI) have been vastly complicated by the differences in regulatory processes and standards, including those relating to burden of proof and confidentiality. Our research institutions appear to be disadvantaged in their compliance efforts by confusion in regard to matters that span ORI, FDA and OHRP jurisdiction, given that IRB and research misconduct proceedings typically are triggered by a common set of events, and that one proceeding can lead rapidly to the commencement of another procedure.

Among the composite scenarios described in presentations to SACHRP by institutional officials have been the following:

- An IRB investigated a situation that arose during a parallel research misconduct proceeding, but IRB findings and penalties (suspension of an investigator from conducting human subjects research for a defined period) long preceded any conclusion reached in the research misconduct process. The IRB made its required report to OHRP, which then replied by accepting the report and, upon receipt of FOIA requests, providing the report to the public. Therefore, the human subject violations that formed an essential component of the potential research misconduct, were already determined and information about those violations publicly available, prior to the conclusion of the research misconduct process.

- In parallel proceedings, and closely related fact patterns, an IRB and a research misconduct process led to findings that noncompliance with Common Rule standards had occurred, but research misconduct allegations were not substantiated. The IRB and the research misconduct process reached different conclusions about the basic facts of what had occurred. The project was supported by a PHS grant. The institution therefore had two differing, conflicting sets of fact findings, and was confused about what to report: reporting the IRB findings to OHRP and PHS would have been consistent with OHRP and PHS requirements, but would have reflected badly on the investigator's integrity; at the same time, respecting the finding that research misconduct had not been substantiated would have preserved the investigator's reputation but would have violated required reporting to OHRP and to PHS, as grant sponsor.

- An IRB investigated fabrication of informed consent documents and related violations of eligibility criteria for enrollment, and then suspended the protocol, requiring the investigator to notify subjects of the study suspension and of the reasons for the suspension. Although the matter was referred also to the research misconduct inquiry process, subjects and co-investigators were advised of the Common Rule regulatory violations – as was OHRP in an institutional letter reporting the suspension – long before any research misconduct process had been completed. The investigator protested, suggesting that his reputation was being ruined before the confidential misconduct process had even passed the inquiry stage.

- In an attempt to preserve the required confidentiality of the research misconduct process, a research integrity official at the institution failed to disclose to the IRB an allegation of research misconduct in an ongoing study with human subjects. At the time the allegation was received, there was no indication that the alleged research misconduct could be placing subjects at any increased risk of harm, but the subsequent research misconduct inquiry and investigation produced evidence that subjects had been placed at increased

risk. Had the IRB known these facts (or had the IRB known enough to have initiated its own investigation), the study would likely have been suspended, but the IRB did not learn of the research misconduct allegation until many months after it had been reported to the research integrity official. Ultimately, the investigation process resulted in a finding that research misconduct in fact had occurred; however, by that point, the study had concluded. Subjects had been exposed to risks in a discredited study.

These are only a few examples of the many ways in which applying Common Rule standards and OHRP guidelines can become enormously complex when the allegations also suggest possible research misconduct.

### 3. Specific Issues Requiring Clarity

Among the specific questions that SACHRP suggests merit official guidance are the following:

- Does a sufficiently credible and specific allegation of misconduct in research involving human subjects qualify as an "unanticipated problem involving risks to subjects or others or any serious or continuing noncompliance" that requires prompt reporting to OHRP?

- How should the IRB, the research integrity officer and the institutional official interact with one another about serious allegations received in which both human subjects and research misconduct issues are implicated? Given regulatory requirements of confidentiality in the research misconduct process,[1] should a research integrity officer advise the institutional official and the IRB of allegations that relate to human subjects protections, and if, so, at what point in the research misconduct process?

- When records and data have been sequestered, as required, in a research misconduct proceeding, what access should an IRB have to those materials, when they are needed for a related IRB inquiry?

- For OHRP reporting purposes, corrective actions, and notification to subjects, what should an IRB do if IRB determinations are made prior to or the determinations differ from final research misconduct findings on the same factual issues?

[1] See 42 CFR 93.108: "Disclosure of the identity of respondents and complainants in research misconduct proceedings is limited, to the extent possible, to those who need to know, consistent with a thorough, competent, objective and fair research misconduct proceeding, and as allowed by law."

- To what extent should IRB determinations of serious noncompliance be factored into an institution's responsibility to "protect or restore" the reputation of an investigator who has been cleared of closely related research misconduct allegations?

- How should a research misconduct proceeding treat an IRB finding that alleged noncompliance with Common Rule standards was not substantiated, when the research misconduct process yields differing determinations on essentially the same evidence? Should it matter to the analysis of this question that the research misconduct process employs a specified standard of proof ("preponderance of the evidence")?

  What considerations should IRBs use in determining whether and how research subjects should be informed if falsification or fabrication of data has been identified, or if research misconduct has been conclusively determined, in a study in which the subjects participated?

  4. Investigation and Sanctions Process for Investigators Accused of Serious Violations of Human Subjects Regulations

As noted previously, OHRP generally enforces Common Rule standards against institutions, while ORI and FDA typically impose sanctions against individual investigators rather than against research institutions, unless they also find failings in an institution's internal processes. SACHRP understands that OHRP does have the authority to refer egregious cases of violations of human subjects regulations in HHS-funded research to the Secretary for consideration of enforcement actions against individual investigators, such as debarment from applying for or benefiting from HHS research funds. However, SACHRP also understands that this authority has never been exercised by OHRP. Furthermore, this enforcement pathway may not formally incorporate due process protections for investigators who are accused of serious and intentional violations of human subjects regulations.

The situation outlined here creates a serious inconsistency in how the Department addresses various ways in which individual investigators may deviate from professional standards of conducting research . On the one hand, the Department has the ability, through ORI, to sanction a PHS-funded researcher who is found, after an ORI process, to have engaged in research misconduct (i.e., fabrication, falsification or plagiarism (FFP)), and through the FDA, to sanction an investigator who violates FDA regulations. On the other hand, it is much less obvious how the Department can, and under what circumstances the Department should, sanction an individual investigator who engages in serious violations of HHS human subjects regulations. This leads to the possibility, for example, that a PHS sponsor such as the NIH might be unaware of an investigator's history of serious and intentional violations of human subjects regulations

when considering a grant application from that individual. This apparent gap is difficult to defend, may lead to subject harm, and may jeopardize public trust in the research enterprise should an example of egregious previous violations of human subjects regulations by a PHS-funded investigator come to light.

To address the gap described above, SACHRP recommends that the Department develop a mechanism for investigation of such cases, for imposition of sanctions as indicated, and for communicating the relevant findings to other affected federal agencies when an HHS-funded researcher is accused of serious violations of human subjects regulations. One option might be for OHRP and/or PHS (as a research funder) to develop a mechanism for undertaking such an investigation, for recommending appropriate sanctions, and for developing appropriate communication strategies.

5. FDA Standards and Proposed Mandatory Reporting of Suspected Falsification of Data

In developing guidance for research institutions, it would seem appropriate to include specific consideration of how FDA jurisdiction, standards, processes and enforcement may interact with those of OHRP and ORI. Specifically, SACHRP is mindful of the pending proposal by FDA for adoption of rigorous requirements that sponsors (which would include sponsor institutions) report suspicion of falsification of data in clinical investigations, nonclinical laboratory studies, and clinical studies in animals. 75 Fed. Reg. 7412 (Feb. 19, 2010). Under this proposal, a sponsor that "becomes aware of information indicating that any person has, or may have, engaged in falsification of data" in such studies would be required to report this to FDA within 45 days, so that FDA would have an "early alert to potentially serious lapses in subject protection or data integrity," 75 Fed. Reg. at 7416, and would be able to take swift action to abate any threat.

The difficulty with this approach is directly related to the substance of this letter: this "early warning" by sponsors to the FDA has significant implications for, and would interact in complex ways with, existing institutional processes for protecting human subjects, for preserving the reputation of the respondent, and for investigating allegations of research misconduct. FDA actions, if taken quickly in response to such a report, could significantly complicate IRB actions and institutional research misconduct proceedings, in ways that are not completely clear but whose outlines are already suggested by the difficulties in reconciling OHRP with ORI processes and standards. Having a third set of standards that also could apply in these settings would yield additional complexity and confusion, unless regulations and guidance clearly indicate how all three sets of standards might be applied in a coordinated, non-disruptive way.

In light of this pending FDA proposal, the questions raised by SACHRP in this letter are timely indeed, and should be addressed before additional complexity is added to an already confusing regulatory regime. SACHRP's concerns in this regard were, in fact, voiced by multiple institutions and persons that commented on the proposal when it was originally published in the Federal Register, with many comments indicating that a strict reporting FDA standard could wreak havoc on established institutional IRB and research misconduct processes.[2]

Finally, SACHRP notes that some research projects funded by various offices and agencies within HHS may be co-supported by, and/or share professional staff and resources with, research projects funded by other agencies of the United States government. In the process of addressing the issues raised in this letter, HHS may therefore wish to consider how HHS-mandated processes and standards for research misconduct may be inconsistent with the various analogous processes and standards of these other agencies.

[2] See, e.g., *Comments of the Association of American Universities and Council on Governmental Relations on FDA Proposal for Reporting Information Regarding Falsification of Data*, May 19, 2010.